Adverse Childhood Experiences and Systemic Inflammation in Adults in the United States

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Abstract

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Background and significance: Adverse childhood experiences (ACEs) are associated with poor behavioral and physical health outcomes in adulthood. Though not fully elucidated, systemic inflammation is one mechanism through which ACEs are thought to affect health outcomes in adulthood. The objective of this study was to assess the relationship between ACEs and systemic inflammation and if this relationship differed by participant sex, race/ethnicity, sexual orientation, or parent age, income, and education.

Methods: The sample was the 9,161 participants who completed Waves I, III, and IV of the National Longitudinal Study of Adolescent to Adult Health and had a valid measurement for C-reactive protein (CRP), an indicator of systemic inflammation. The exposure was an ordinal ACE score developed from a 6-item questionnaire administered at Wave III of the study. Multivariable linear regression of log-transformed CRP (log CRP) concentration on ACE score was performed with covariates for adjustment and interaction.

Results: ACE score was not significantly associated with log CRP in crude or adjusted linear regression models and no evidence of interaction was present.

Discussion: These findings do not support an association between ACEs and systemic inflammation. This finding adds to the heterogeneous landscape of association of ACEs with CRP and emphasizes the need for consistent indicators of biological embedding to clarify the relationship between ACEs and poor health in adulthood.

Introduction

Background and significance

Substantial evidence has linked early life adversity and stress with poor outcomes in adulthood. These stressors, termed adverse childhood experiences (ACEs) are pervasive, and the in 2018, U.S. Centers for Disease Control and Prevention estimated that as much as 61% of the US population has been exposed to 1 or more ACEs.[1,2] Broadly, ACEs are categorized as household dysfunction or maltreatment.[3] Household dysfunction includes exposures such as parental divorce, witnessing illicit drug use, or intimate partner violence in the home; whereas, maltreatment events include emotional, physical, or sexual abuse.[3] ACEs tend to cluster with worse social determinants of health (physical and sexual abuse are significantly associated with living in poverty).[4] Certain demographic groups such as racial/ethnicity minorities, female sex, and minority sexual orientations are also at greater risk of ACEs providing significant equity and social justice justification for their further evaluation in individuals from these groups.[2,5–8] Those who identify as sexual minorities are at higher risk of exposure to ACEs as well as a higher risk for a variety of adverse outcomes including earlier sexual debut, poor adult mental health, HIV risk behaviors, suicidal ideation and attempts, and disability compared to their cisgender and heterosexual peers.[6,8–10]

Exposure to these early life traumas has been associated with not only mental and behavioral disorders but chronic, age-related diseases including diabetes, cardiovascular disease, cancers, and autoimmune conditions.[11,12] These outcomes also tend to cluster along with parental demographics such as socioeconomic status reflected by education and income. Increasing evidence also suggests parent age at birth may result in differing susceptibility to age-related diseases due to rearing and/or epigenetic differences of parents from different age cohorts.[13,14]

The ubiquity of these outcomes and the burdens they place on individuals and health systems motivates increased understanding of the determinants and mechanisms that underlie them.

One of the prevailing hypotheses involve chronic stress, including ACEs that lead to a disruption of allostasis or "the [normal] operating range, and the ability of the body to increase or decrease vital functions to a new steady state on challenge."[15] This change in allostasis as a result of stress is the first step leading to what is referred to as multisystem dysregulation or allostatic overload.[11,16–21] Disentangling the milieu of factors contributing to this dysregulation takes substantial interdisciplinary research. Compelling evidence from a variety of study designs identifies chronic, inflammation as one of the primary mediating factors in the etiology of chronic diseases. Previous twin-studies support this hypothesis, demonstrating differences in neuroanatomy, immune response, and metabolism between twins who differed in exposure to ACEs.[22–25] In a large, representative biomarker study, Hostinar and colleagues found 12-hour urinary catecholamine neurotransmitter excretion was a significant mediator of a positive significant association between ACEs and inflammation. Previous studies using functional magnetic resonance imaging have also demonstrated significant increases in neuronal activity in a region of the brain positively associated with major depression after delivery of the cytokine interferon-alpha and related to increased cytokine concentration following vaccination.[26–28] Additionally, animal studies of rats have indicated that maternal rearing behavior can result in epigenetic modifications and transcriptional changes on glucocorticoid receptors that persist into adulthood and associated with impaired learning and fear response.[29–31]

In their seminal review, McEwen and Stellar identified five interdependent mechanisms by which stress can lead to increased inflammation and why certain individuals are more or less predisposed to such outcomes including behavioral processing, individual neurochemistry,

endocrine regulation, accumulation of neuronal damage, and immune mediation.[11] Briefly, behavioral processing is the cognitive appraisal of a stimulus as noxious or benign and the identification of an appropriate, graded response. Neurochemical differences, including diminished neuronal serotonin levels have been implicated in impaired behavioral processing, leading to either apathetic or hyperreactive responses which may independently result in subsequent physical trauma or relational stressors.[7,8] These changes in affect and response are concomitant with neuroanatomical changes and damage such as decreased hippocampal volume and greater amygdala activation.[34,35] In addition, chronic stress is known to cause dysfunction of the endocrine regulation of hypothalamic-pituitary-adrenal (HPA) axis through blunting of cortisol's diurnal rhythm, epigenetic and subsequent transcriptional changes to the glucocorticoid receptor gene, and elevated cortisol secretion.[18,36–39] This chronic elevation of cortisol increases efflux of glucose, resulting in feedback in which insulin secretion is also increased to compensate for elevated glucose trafficking. Hyperinsulinemia, a hallmark of type II diabetes, is known to result in hyperlipidemia and increased adiposity, two inflammatory states thought to be potential mediators through which stress "gets under the skin" or undergoes biological embedding.[40]

While the theoretical effects and therefore, evidence of such biological embedding through inflammation are wide-ranging, strong evidence supports the use of serum biomarkers for measuring systemic inflammation. Typical biomarkers include white blood cell count and common cytokines, such as, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP).[41–44]. CRP is an acute-phase reactant of the innate immune system secreted in high quantity in response to stimulation by IL-6 from acute injury or infection.[45,46]

Elevated CRP has also been linked to atherosclerosis, hypertension, diabetes, and depression, diseases also linked to acute and chronic stressors such as ACEs.[26,47–51]

To our knowledge, this is the first longitudinal cohort study to assess the association between ACEs and CRP in a large, representative sample of U.S. adults. Previous studies have relied on retrospective study designs wherein subjects were asked about their prior ACE exposure at or around the time of biomarker collection or relied on non-U.S. study populations.[40,52] This study is strengthened by the robust sample and study design of the National Longitudinal study of Adolescent to Adult Health (Add health).

Objective

The aims of this study were to: (1) Investigate the association between ACEs measured in early adulthood and subsequent inflammation and (2) test if this association is modified by race/ethnicity, sex, sexual orientation, parental income, parental age, and parental education. The purpose of this study, examining ACEs and inflammation using data from a nationally representative cohort of U.S. adults was to add evidence describing underlying mechanisms linking ACEs with adverse health outcomes and to contribute to clinical and public health practitioners' abilities to intervene and mitigate the deleterious outcomes associated with ACEs. Our hypothesis was that greater exposure to ACEs would be associated with greater CRP and that this association would differ between participants based on race/ethnicity, sex, sexual orientation, parental income, parental age, and parental education.

Methods

Study Design

Add health is a school-based nationally representative cohort study. As of December 2019, five waves of data collection have been completed (Wave I, 1994-95; Wave II, 1996; Wave III, 2001-02; Wave IV, 2008; Wave V 2016-18). The Add Health sampling methodology is a clustered approach at the high school level using systematic sampling methods and implicit stratification with unequal probability weighting. Wave I of Add Health was administered in 80 high schools and 52 middle schools obtained from a database developed by Quality Educational Data, Inc. to ensure representativeness based on region, urbanicity, school attendance, school type, and population.[53] Contextual data was also collected from academic peers, school administrators, romantic partners, and other family members. Subsequent waves have been completed via in-home participant interviews.

Participants

A clustered sample of 90,118 children and adults in 7^{th} – 12^{th} grade who attended participating schools comprised the Wave I sample in addition to 144 school administrators, 20,745 academic peers, and 17,670 parents. The final study population was made up of the sample of participants who completed Waves I, III, and IV who had a valid Wave IV serum CRP measurement. All participants provided informed consent for participation and the study was approved by the Institutional Review Boards of the University of North Carolina and University of Washington.

Exposure

The exposures of interest were ACEs. During Wave III in-home interviews, at which point participants were between 18 – 26 years old, they were asked about the number of times

they had experienced maltreatment by adults prior to 6th grade. The instrument was introduced by the interviewer stating: *"By the time you started 6th grade how often had…."* Each item then probed a specific ACE by continuing with the following queries:

- *"...your parent or other adult care-givers left you home alone when an adult should have been with you,"*
- *"...your parent or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing,"*
- *"...your parent or other adult care-givers slapped, hit, or kicked you,"*
- *"...your parent or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations,"*
- *"...Social Services investigated how you were taken care of or tried to take you out of your living situation,"* and
- *"...you actually been taken out of your living situation by Social Services?"*

The instrument was based on the original ACE study which included items assessing household dysfunction and caretaker maltreatment.[3]

ACEs were specified in three ways: ACE type indicator variables, composite ACE score, and dichotomized ACE score. The ACE type indicator variable was constructed using the following criteria: If a participant endorsed having 1 or more ACE events within a single category, the participant was defined as positive for the corresponding ACE, with the following categories: left alone, basic needs not met, physical abuse, sexual abuse, any social services involvement, and removed by social services. The ACE score was then calculated based on the sum of positive ACE type indicator variables with a possible range of 0-6. This score was then condensed to a scale of 0-4+ ACEs to account for small numbers in the upper ACE exposure range. The dichotomized ACE score was constructed from the composite ACE score.

Dichotomous ACE exposure was defined as low or high exposure based on whether a participant's composite ACE score was ≤ 1 or >1, respectively. All other variables were included as indicators to allow for greatest flexibility in adjustment for regression models.

Outcome

The primary outcome of interest was systemic inflammation measured by high sensitivity C-reactive protein assay. During the in-home portion of Wave IV, Add Health researchers collected finger prick blood samples as blood spots using sterile, single-use lancets and collection paper. These samples were then quantitatively evaluated for CRP using enzyme-linked immunosorbent assay (ELISA).[54] Ninety-four participants with CRP levels below the limit of detection (0.082 mg/L) and those whose levels were greater than four standard deviations above the mean were excluded from our analyses to ensure data quality. CRP was log-transformed (log CRP) to ensure normality and treated as a continuous variable. CRP was also used as a dichotomous outcome variable as elevated and low/normal based on a serum concentration of ≥3 mg/dL cutoff. The 3 mg/dL threshold was selected because of its common application in clinical settings.[42,45]

Covariates

Our analysis included various demographic covariates including participant race/ethnicity, sex, and sexual orientation. Parental covariates age, household income, and total education attained were also included. The instruments containing participant race/ethnicity and sex were administered during Wave I. All parental covariate responses were obtained from parent interview also administered in Wave I.

Race/Ethnicity: Participants were asked to indicate whether they belonged to each of the following racial categories: American Indian or Native American, Asian or Pacific Islander,

Black, White and other and whether they were of Hispanic ethnicity, whether they identified as a member of that particular group. We constructed a variable wherein, if a participant endorsed only one racial identity the corresponding level was indicated. Participants who identified as more than one race were coded as other as were American Indian or Native American, Asian or Pacific Islander, and those who reported "other" race. Race/ethnicity was then stratified into Non-Hispanic Black, Non-Hispanic White, Non-Hispanic Other, and Hispanic.

Sex: Participants biological sex was a dichotomous variable (female, male).

Sexual orientation: Participant sexual orientation was collected in Wave IV of Add Health, responses included: straight, mostly straight, bisexual, mostly gay or lesbian, gay or lesbian, and asexual. We then condensed this variable by including those who identified as mostly straight or mostly gay or lesbian into a single bisexual category and dropped those who identified as asexual from our adjustment.

Parental Age: We constructed a 4-level, ordinal variable from continuous parental age on the interview date with the following strata: <30, 30-39, 40-49, ≥50.

Parental Education: Highest education attained by parents was collapsed into a 5-level variable containing the following: did not graduate high school, high school or general education development (GED), some college, college, post-college.

Parental Income: Parental income was included as a constructed ordinal variable with the levels: <$25,000, $25,000-49,000, $50,000-74,999, ≥$75,000.

Statistical methods

All statistical analyses were performed with the R Statistical Package (Version 4.0.1) in RStudio.[55,56] The R package, Survey: Analysis of Complex Survey Samples was used to account for the complex survey and cluster-sampling design effects in descriptive and analytical data.[57,58]

Chi-squared tests were performed to assess distributions of covariates and individual ACE categories with composite ACE score and dichotomous CRP. We also performed univariable, multivariable, and multivariable interaction linear regression of log CRP concentration on composite ACE score to detect if an association exists between composite ACE score and CRP and if this association is significantly modified by two-way interaction between composite ACE score and race/ethnicity, sex, sexual orientation, parental age, parental education, or parental income separately. Regressions were repeated using the dichotomous ACE score. Significance was defined according to $p < 0.05$. Exponentiated crude and adjusted regression estimates were reported along with their 95% confidence intervals as percent difference from reference group. Interaction was present if the interaction term had a significance of $p < 0.05$.

Results

Descriptive data

After excluding all those with missing data, the total sample size was 9,161. As shown in Table 1, of this sample, biological sex was approximately equally represented with 49.3% participants being female. Non-Hispanic whites (65%) were disproportionately overrepresented compared to Non-Hispanic Blacks (15 %), Hispanic (12%), and Other (7%) ethnic and racial group. Most participants identified themselves as straight (86.9%), with only 11.8% identifying as bisexual and 1.3 % identifying as gay or lesbian.

Parent age was approximately normally distributed with 1.7% of participants' parents being under the age of 30, 46.6% between the ages of 30 – 39, 44.0% between ages 40 – 49, and 7.8% were older than 50 at the time of interview. Most parents had either graduated from high school or earned a GED (42.9%). However, 40.3% reported some college or greater education. Only 16.7% of parents reported not graduating high school. About 70% (68.1%) of parents reported a household income of less than $50,000, while 19.6% earned between $50,000 – 74,999 and 12.3% earned more than $75,000 per year. Mean CRP was 3.89 mg/L and 61.4% of the sample had a CRP measurement of less than 3 mg/L. Supplementary results including bivariate chi-squared and Pearson correlation coefficients for each ACE type are available in Sup. Table 1 and 2, respectively.

Main results

Log CRP was not significantly associated with composite ACE score (β = -0.004; 95% CI -0.039, 0.030;) (Table 2). An adjusted model including race/ethnicity sex, sexual orientation, parent age, parent education, and parent income was non-significant for association with composite ACE score (β = -0.012; 95% CI -0.052,0.029;). A third model including all interaction

between composite ACE score with the same covariates was also not significant. When interaction models were fit with each covariate separately along with ACE score on log CRP, none of the interaction terms were significant (Table 4). The comparable estimates with dichotomous ACE score as the predictor were also not significant. A *post hoc* defined multivariable regression of log CRP concentration on all six dichotomous ACE indicator variables was also performed to assess if any ACE category exposure was significantly associated with log CRP. In this analysis, exposure to sexual abuse was the only ACE associated with a significant difference in CRP, with those exposed having 23% (β = 0.214; 95% CI 0.024,0.404;) greater CRP compared to unexposed participants (Table 4).

Discussion

The aims of this study were to determine if an association existed between ACEs and CRP among a representative sample of US adults, and if such an association was modified by demographic covariates including race/ethnicity, sex, sexual orientation, and parent age, education, and income. Our hypothesis was that greater exposure to ACEs, as measured by a cumulative ACE score, would be associated with greater CRP. We also predicted that differences in this association would exist between participants of various demographic characteristics as a result of differences in physiology, socialization, environment, and stress processing.

We found no evidence of significant association between ACEs and CRP, nor did we see evidence of interaction between ACEs and race/ethnicity, sex, sexual orientation, or parental age, education and income. In a *post hoc* model, exposure to sexual abuse was significantly associated with greater CRP after adjusting for exposure to other ACEs. These results must be interpreted with caution considering multiple comparison and this was not part of our apriori analysis. However, this finding is consistent with those of Negriff et al. that demonstrated exposure to sexual abuse to have a greater association with depressive, anxiety, and trauma symptoms compared to those exposed to other ACEs and a meta-analysis by Baumeister et al. in which IL-6 and TNF-α but not CRP were associated with childhood trauma; in this review, subgroup analysis of those participants who had experienced sexual and physical abuse was also suggestive of different types of trauma predicting differential effects on serum cytokines concentrations.[59,60] Rasmussen et al. also identified a significant positive association between ACEs and inflammation measured by IL-6 and soluble urokinase plasminogen activator receptor but not CRP.[61] Among participants of a lifestyle intervention study to examine the effects of

resilience resources, Gouin et al. observed IL-6 to have a significant positive association with ACE exposure whereas CRP did not.[62]

However, numerous previous studies have observed significant associations between ACEs and CRP. In a large Finish cohort of the nationwide Health and Social Support (HeSSup) Study, Runsten et al. identified significant interaction between levels of social support and ACEs on CRP but no significant main effect after adjusting for age and body mass index.[63] Though, CRP was not individually reported, a composite inflammatory factor including CRP along with IL-6, fibrinogen, E-Selectin, and ICAM-1 was significantly associated with ACEs among participants of the Midlife in the United States (MIDUS) Biomarker Project.[52] Additionally, de Punder et al. presented findings from a study of German psychiatric hospital patients indicating significantly higher levels of inflammation measured by leukocyte count, IL-6, and CRP among those exposed to ACEs with and without major depressive disorder compared to those with neither.[64] Findings from the Dunedin Multidisciplinary Health and Development Study in New Zealand have also indicated significantly greater risk of elevated CRP among those with definite childhood maltreatment and high levels of childhood isolation but not major depression alone.[65,66] Chen and Lacey also identified a significant positive graded relationship among participants of the Nation Child Development Study in the United Kingdom between ACEs and CRP.[67]

The results of our study did not support our stated hypotheses. However, our *post hoc* finding that exposure to sexual abuse was significantly associated with higher levels of CRP provides additional evidence to support the substantial negative psychological and physiological impacts of sexual trauma relative to other ACEs and highlights an important current limitation in this field.[60] This limitation is that definitive quantitation of ACEs and other experiences as

exposures is not possible. This leads to the simplification of very complex phenomena into a set or sum of dichotomized exposures. As was done in our study, the most common technique is to generate a cumulative score for ACE exposure based on a dichotomous indicator of whether a study participant had experienced an ACE of a certain type (e.g. parental absence, physical or sexual abuse). Though this technique has high utility due to its simplicity, ease of implementation, and standard usage, it is limited in the ability to make individual inference due to the heterogeneity of responses to trauma and personal processing of such events. This violates the consistency assumption put forth by the potential outcomes framework of causality.[68]

Additionally, the magnitude of an individual's exposure to any particular ACE is lost by dichotomizing the exposure. The validity of this method has further been critiqued in a recent study by Negriff, in which adolescent mental and behavioral health symptoms were evaluated according to exposure to ACEs by type (maltreatment and household dysfunction) and item.[60] The results indicate that the effect of ACEs on mental and behavioral symptoms is heterogeneous, making the case for evaluating the effects of ACEs independently rather than in aggregate.[60]

Other efforts to analyze ACEs have relied on such methods as latent class or principal component analysis and hierarchical modeling but have not been widely implemented.[61,69] Such methods may allow for more accurate analyses by making more efficient use of data and/or implementing methods able to identify of more complicated exposure-outcome relationships. However, these benefits come at the cost of computational and interpretative simplicity. Also, given the importance of hypothesis driven approaches for confirmatory studies, latent-class methods may be more appropriate for exploratory analyses given their less well-defined hypotheses.

The discordant results from other studies have also revealed that CRP may be unreliable indicator of systemic inflammation. While numerous studies have demonstrated a significant association between ACEs and CRP, such effect sizes are often small and no longer significant after adjusting for body mass index (BMI) and smoking status. [61,70] We chose to omit these covariates from our analysis due to them possibly mediating a relationship between ACE exposure and inflammation. Furthermore, interpretation of CRP levels is nontrivial. Though previous work has demonstrated CRP to be a valuable marker for cardiovascular disease and acute bacterial infection, population averages for CRP are inconsistent and for reasons that remain unclear differ by sex, race/ethnicity, and age.[42,45,71,72] The nonspecific nature of CRP in the immune response may reflect its ability to integrate information from both short and long-term stressors, thereby impeding our ability to make strong inference about either type of exposure. Lastly, CRP was collected from dried whole blood spots rather than whole blood. Though, this method has been well validated, the small differences in accuracy (0.11 – 0.21 mg/L) may reflect enough random variation to obscure an effect of small magnitude.[73]

Our sample was a subset of Wave IV Add Health participants between the ages of 24 – 32 at the time of CRP measurements.[53] In contrast, previous studies have used samples of varying ages from 9 – 80 years at the age of CRP measurement.[67,74–77] Since age is positively correlated with CRP, it is important that age be accounted for when using CRP as an indicator. This presents a challenge due to many large studies recruiting participants of a small age range, including the 1958 British Birth Cohort,[78] English Longitudinal Study of Aging,[79] Dunedin Multidisciplinary Health and Development Study,[80] and Avon Longitudinal Study of Parents and Children,[81] all of which have been used to address the association between ACEs and CRPs using cross-sectional study designs. [67,74–77] The inability to adjust for participant age in these

existing cohorts impedes the ability to make cross-study comparisons when study populations are from different age or period cohorts. Based on this, interaction between participant age and ACEs in our study may be a possible explanation for the apparently conflicting results of this and other studies. We chose not to include participant age as a covariate due to the relatively narrow age range of Add health participants.

Though the results of this study may not demonstrate significant associations between ACEs and CRP, they are nonetheless informative. There are many plausible explanations for our findings including differences in social cohesion, diet, and health behaviors that have been identified as contributors to inflammation via mechanisms that are not well understood.[74,82] Notably, Add Health also only examined a subset of ACEs from the questionnaire used by the original ACE study in addition to two further questions about involvement with social services.[3] Participants were also asked to indicate the number of times an ACE had happened rather than simply if they had an ACE. It is possible these deviation from what has commonly been done to examine ACEs are responsible for the difference in results. Although analytical attempts were made to transform the data into a similar format, response differences due to participant question appraisal may remain and bias the results.

Another possibility is that unmeasured environmental exposures which contribute to psychoneuroendocrine changes such as industrial pollutants or endocrine disrupting chemicals (EDCs), found widely in consumer products, have masked an association.[83] Due to poorer regulatory supervision and fewer use restrictions, such exposures are more common in the U.S. than in other upper and middle income countries and may contribute to obscuring a true association. Finally, though previous studies have indicated reliability, social desirability or other

biases affecting ACE characterization due to cultural or environmental differences between Add Health participants and subjects of prior studies cannot be completely disregarded.[84]

Strengths and Limitation

The results of this study may be generalizable to the United States general population if not a reflection of unidentified bias. One important limitation of this study as described previously is the use of a composite ACE score, done for the sake of coherence with previous literature and ease of interpretation. Another limitation is CRP test variability due to some differences in reliability of blood spot versus whole blood assay, as well as its quality as an indicator of chronic systemic inflammation given the mixing of acute and chronic insults. The large sample size, Add Health's sampling methodology and study design to ensure representation of the U.S. population, as well as robust analytical tools for complex surveys, however, are all strengths of our study despite the somewhat surprising results.[53,85] Furthermore, these results reinforce a need for additional, more consistent indicators of biological embedding to illuminate the relationship between ACEs and poor health in adulthood.

Tables

Table 1 – Participant Characteristics by Composite Adverse Childhood Experience Score

National Longitudinal Study of Adolescent to Adult Health

	Composite ACE Score					Overall	N = 9161
	0	1	2	3	4+		
Sex, %							
Male	50.64	49.28	51.60	53.77	56.86	50.71	4383
Race/Ethnicity, % (SD)							
Hispanic	11.78 (0.32)	11.16 (0.32)	14.49 (0.35)	14.73 (0.36)	11.36 (0.32)	12.05 (0.33)	1502
Non-Hispanic Black	15.58 (0.36)	12.67 (0.33)	15.12 (0.36)	16.92 (0.38)	22.83 (0.42)	15.07 (0.36)	1864
Non-Hispanic White	66.45 (0.47)	67.86 (0.47)	60.44 (0.49)	58.71 (0.49)	58.83 (0.50)	65.68 (0.48)	4754
Non-Hispanic Other	6.19 (0.24)	8.31 (0.28)	9.95 (0.30)	9.64 (0.30)	6.98 (0.26)	7.30 (0.26)	1005
Missing							36
Sexual orientation, % (SD)							
Straight	88.19 (0.32)	85.87 (0.35)	84.86 (0.36)	82.02 (0.38)	85.09 (0.36)	86.91 (0.34)	7896
Bisexual	10.56 (0.31)	12.73 (0.33)	13.93 (0.35)	15.96 (0.37)	14.51 (0.35)	11.81 (0.32)	1082
Gay or lesbian	1.24 (0.11)	1.39 (0.12)	1.21 (0.11)	2.01 (0.14)	0.39 (0.06)	1.28 (0.11)	113
Missing							70
Parent Age, %							
< 30	1.29	2.04	1.81	2.82	3.75	1.66	111
30 – 39	44.65	46.60	50.89	58.77	51.18	46.55	3498
40 – 49	45.86	44.03	41.03	32.06	34.60	44.04	3587
≥ 50	8.20	7.33	6.26	6.35	10.46	7.75	680
Missing							1285
Parent Income, %							
< $24,999	30.99	27.50	34.10	41.84	57.15	31.56	2131
$25,000 – 49,999	36.35	37.22	37.92	35.54	36.35	36.51	2564
$50,000 – 74,999	19.98	21.26	18.22	18.36	19.98	19.63	1340
≥ $75,000	12.68	14.02	9.76	4.26	12.68	12.30	858
Missing							2268
Parent Education, % (SD)							
Did not graduate HS	17.08 (0.38)	13.90 (0.35)	17.50 (0.38)	21.27 (0.41)	26.43 (0.44)	16.75 (0.44)	1335
HS Graduate or GED	43.41 (0.50)	42.39 (0.49)	41.34 (0.49)	44.81 (0.50)	39.47 (0.49)	42.87 (0.49)	3070
Some College	17.95(0.38)	19.11 (0.39)	19.71 (0.40)	21.97 (0.41)	15.86 (0.37)	18.54 (0.37)	1525
College	12.79 (0.33)	15.51 (0.36)	13.67 (0.34)	7.59 (0.27)	11.65 (0.32)	13.33 (0.32)	1190
Post-college	17.08 (0.28)	13.90 (0.29)	17.50 (0.27)	21.27 (0.20)	26.43 (0.25)	8.51 (0.25)	766
Missing							1275
C-Reactive Protein							
mg/L, *mean (SD)*	3.94 (5.28)	3.74 (5.01)	3.93 (5.00)	4.26 (5.45)	3.64 (4.50)	3.89 (5.17)	-
≥ 3 mg/L, % (SD)	38.21 (0.49)	38.56 (0.49)	40.55 (0.49)	38.96 (0.49)	37.90 (0.49)	38.59 (0.49)	-

*Percentages based on survey weight estimates, N is raw number of participants

Table 2 – Nested Regression estimates for Composite ACE Score and C-Reactive Protein

Concentration

	Model 1: Crude			Model 2: Adjusted			Model 3: Adjusted with Interaction		
	Estimate*	Lower 95% CI	Upper 95% CI	Estimate*	Lower 95% CI	Upper 95% CI	Estimate*	Lower 95% CI	Upper 95% CI
Intercept	87.8	76.8	99.4	334.9	180.1	487.1	339.3	148.4	505
Composite ACE Score	-0.4	-3.8	3.0	-1.2	-5.2	2.9	-3.4	-22.9	39.1
Sex									
Female				Ref	Ref	Ref	Ref	Ref	Ref
Male				-41.1	-45.5	-36.2	-41.7	-47.3	-35.6
Race/Ethnicity									
Hispanic				Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black				-1.0	-15.6	15	-2.0	-19.7	20.9
Non-Hispanic White				-4.9	-18.1	10.5	-9.5	-25.2	10.5
Non-Hispanic Other				-16.5	-30.9	1.0	-20.6	-36.9	1.0
Sexual orientation									
Straight				Ref	Ref	Ref	Ref	Ref	Ref
Bisexual				-1.0	-12.2	12.7	3.5	-10.4	19.7
Gay or lesbian				-18.9	-41.1	11.6	-9.5	-40.5	37.7
Parent Age									

<30		Ref	Ref	Ref	Ref	Ref	Ref
30-39		-25.2	-46.2	4.1	-24.4	-48.8	12.7
40-49		-30.2	-49.8	-2.0	-26.7	-50.3	7.3
>50		-18.9	-42.9	13.9	-13.9	-42.3	28.4
Parent Education							
Did not graduate HS		Ref	Ref	Ref	Ref	Ref	Ref
High school or GED		-3.9	-18.1	12.7	-5.8	-22.9	13.9
Some College		-22.1	-33.0	-8.6	-28.8	-40.0	-13.9
College		-16.5	-29.5	-1.0	-17.3	-33.0-	2.0
Post-college		-25.9	-38.7	-10.4	-29.5	-44.0	-11.3
Parent Income							
<$25,000		Ref	Ref	Ref	Ref	Ref	Ref
$25,000-49,999		-3.9	-14.8	7.3	-2.0	-14.8	12.7
$50,000-74,999		-20.5	-30.9	-7.7	-14.8	-27.4	1.0
>$75,000		-19.7	-31.6	-4.9	-18.9	-33.6	-1.0
Interaction Terms							
ACE Score x Sex							
Male					2.0	-5.8	9.4
ACE Score x Race/Ethnicity							
Non-Hispanic Black					1.0	-13.9	18.5
Non-Hispanic White					6.2	-7.7	22.1
Non-Hispanic Other					7.3	-11.3	29.7
ACE Score x Sexual orientation							
Bisexual					-4.9	-14.8	5.9
Gay or lesbian					-14.8	-39.3	19.7
ACE Score x Parent Age							
30 39					-1.0	-24.4	29.7
40 49					-5.8	-27.4	23.4
>50					-9.5	-33.0	23.4
ACE Score x Parent Education							
High school or GED					2.0	-8.6	13.9
Some College					11.6	-3.9	29.7
College					1.0	-13.1	16.2
Post-college					8.3	-9.5	31.0
ACE Score x Parent Income							
$25,000-49,999					-3.0	-11.3	6.2
$50,000-74,999					-9.5	-19.7	3.0
>$75,000					0.00	-15.6	18.5

*Percent change from reference group

Table 3 – Non-Nested Regression estimates for Composite ACE Score and C-Reactive Protein Concentration

Model	Estimate*	Lower 95% CI	Upper 95% CI
ACE Score x Sex			
Composite ACE Score	-0.80	-6.01	4.71
Female	Ref	Ref	Ref
Male	-41.61	-46.15	-36.68
ACE Score x Male	1.51	-5.16	8.65
ACE Score x Race/Ethnicity			
Composite ACE Score	-10.06	-19.59	0.60
Hispanic	Ref	Ref	Ref
Non-Hispanic Black	-11.13	-26.21	7.04
Non-Hispanic White	-26.14	-38.37	-11.49
Non-Hispanic Other	-35.60	-48.11	-20.07
ACE Score x Non-Hispanic Black	8.65	-5.45	24.73
ACE Score x Non-Hispanic White	13.09	0.20	27.76
ACE Score x Non-Hispanic Other	11.85	-3.92	30.21
ACE Score x Sexual Orientation			
Composite ACE Score	-0.30	-3.25	4.08
Straight	Ref	Ref	ref
Bisexual	19.48	5.34	35.53
Gay or lesbian	-14.44	-40.67	23.49
ACE Score x Bisexual	-3.25	-11.13	5.44
ACE Score x Gay or lesbian	-13.84	-34.03	12.64
ACE Score x Parent Age			
Composite ACE Score	11.29	-9.88	37.30
<30	Ref	Ref	Ref
30-39	-15.55	-39.35	17.70
40-49	-21.96	-44.18	9.09
>50	-15.55	-40.49	19.96

ACE Score x 30-39	-8.61	-26.61	13.66
ACE Score x 40-49	-14.36	-31.13	6.50
ACE Score x >50	-15.63	-35.66	10.74
ACE Score x Parent Education			
Composite ACE Score	-3.82	-11.04	3.98
Did not graduate HS	Ref	Ref	Ref
High school or GED	-10.60	-23.20	4.08
Some College	-31.95	-41.55	-20.78
College	-29.46	-40.31	-16.64
Post-college	-39.23	-48.00	-28.97
ACE Score x High school or GED	2.74	-7.04	13.43
ACE Score x Some College	9.86	-2.76	24.11
ACE Score x College	-0.20	-12.72	14.22
ACE Score x Post-college	1.61	-12.01	17.23
ACE Score x Parent Income			
Composite ACE Score	0.10	-5.64	6.08
<$25,000	Ref	Ref	Ref
$25,000-49,999	-10.33	-21.65	2.53
$50,000-74,999	-23.66	-35.40	-9.88
>$75,000	-30.93	-41.84	-17.96
ACE Score x $25,000-49,999	-1.29	-9.43	7.57
ACE Score x $50,000-74,999	-7.32	-17.63	4.19
ACE Score x >$75,000	1.92	-13.67	20.32
*Percent change from reference group			

Table 4 –Regression Estimates for CRP on ACE Indicators

	Estimate*	Lower 95% CI	Upper 95% CI
Left alone	0.00	-7.69	8.33
Basic needs not met	-7.13	-20.07	7.79
Physical Abuse	-1.88	-11.13	8.33
Sexual Abuse	**23.86**	**2.43**	**49.78**
Any Social Services	-7.69	-28.18	18.65
Removed by Social Services	2.74	-25.47	41.48

*Percent change exposed/unexposed, Boldface font indicates $p < 0.05$

Supplementary Data

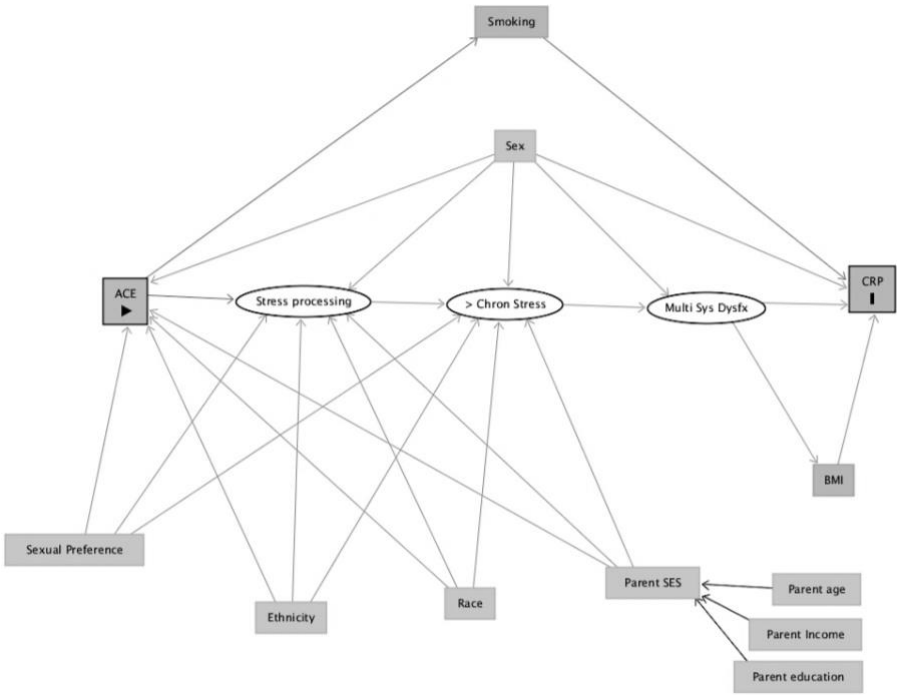
Sup. Table 1 – Individual Adverse Childhood Experience by Composite ACE Score

%	ACEs 1	2	3	4+	Overall	p*
Left alone	60.63	88.99	89.25	98.55	31.28	<0.001
Basic needs not met	4.49	25.31	69.37	88.93	9.12	<0.001
Physical Abuse	31.81	72.67	88.66	97.21	22.3	<0.001
Sexual Abuse	1.12	4.84	20.92	76.62	3.73	<0.001
Any Social Services	1.96	6.54	24.20	51.50	3.57	<0.001
Removed by Social Services	-	1.65	7.60	31.44	1.34	<0.001
*Chi-squared p-values displayed						

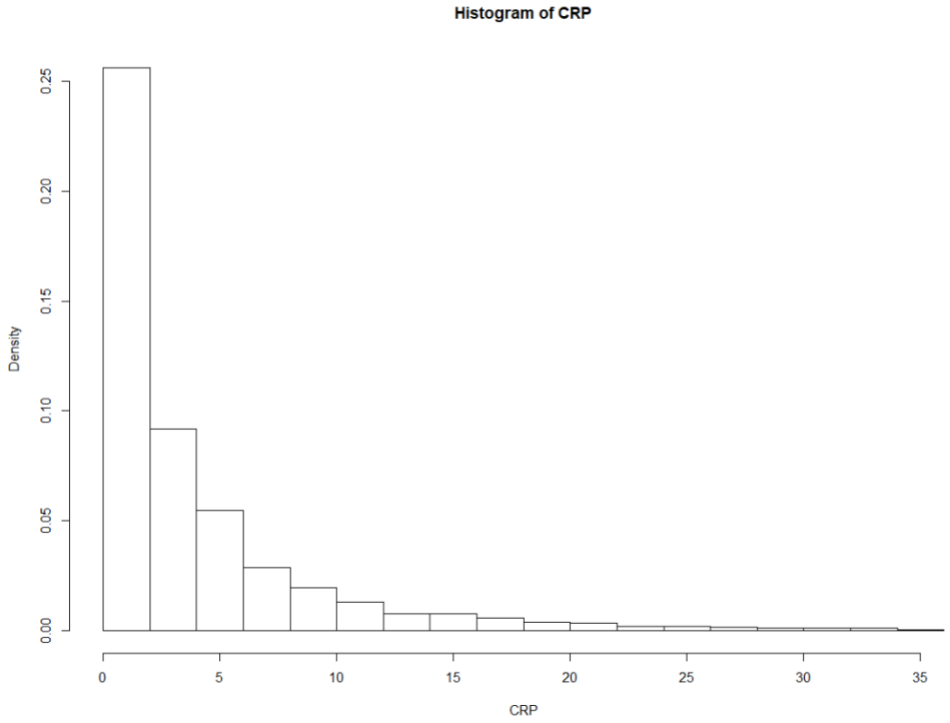
Sup. Table 2 – Adverse Childhood Experience Correlation Table

Correlation (95 % CI)	Left alone	Basic needs not met	Physical Abuse	Sexual Abuse	Any Social Services
Left alone	**1.00**				
Basic needs not met	0.23 (0.21, 0.25)	**1.00**			
Physical Abuse	0.28 (0.26, 0.30)	0.16 (0.14, 0.18)	**1.00**		
Sexual Abuse	0.12 (0.10, 0.14)	0.20 (0.16, 0.24)	0.19 (0.17, 0.21)	**1.00**	
Any Social Services	0.11 (0.09, 0.13)	0.14 (0.11, 0.17)	0.15 (0.13, 0.17)	0.19 (0.14, 0.24)	**1.00**
Removed by Social Services	0.05 (0.03, 0.07)	0.10 (0.07, 0.13)	0.06 (0.04, 0.08)	0.18 (0.12, 0.24)	0.44 (0.26 – 0.62)
*Pearson Correlation					

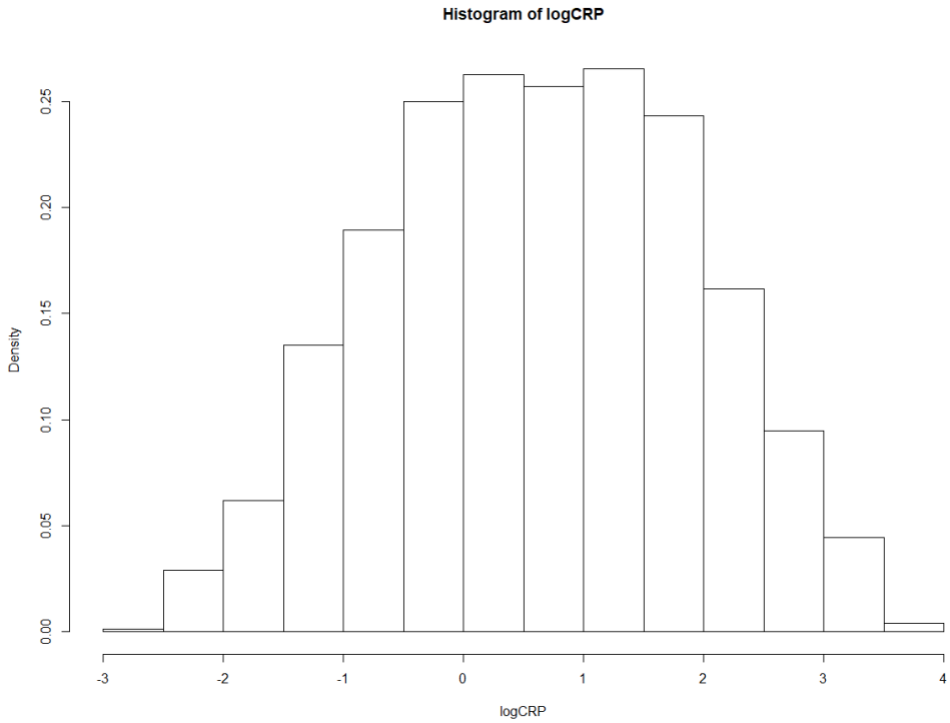
Sup. Figure 1 – Directed Acyclic Graph of Adverse Childhood Experiences and C-Reactive Protein



Sup. Figure 2 – Histogram of CRP Density



Sup. Figure 3 – Histogram of Log-transformed CRP Density



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